PNRR Missione 4, Componente 2, Investimento 1.4 "Potenziamento strutture di ricerca e creazione di "campioni nazionali di R&S" su alcune Key Enabling Technologies"
Iniziativa finanziata dall'Unione europea –- NextGenerationEU.

National Center for Gene Therapy and Drugs based on RNA Technology
Sviluppo di terapia genica e farmaci con tecnologia a RNA

Codice progetto MUR: **CN00000041** – CUP UNINA: **E63C22000940007**

Doctorate of National Interest
RNA THERAPEUTICS AND GENE THERAPY

TITLE OF THE RESEARCH PROJECT
Development of PEG-sheddable stimuli-sensitive NPs targeted to the CD44 receptor able to accumulate in cancer cells

SELECT ONE OF THE FOLLOWING RESEARCH AREA:
☐ **Mechanisms of Diseases and Drug Target Identification**
☒ **Design and Delivery of New Gene Therapy and RNA-Based Medicines**
☐ **Validation and Safety In Preclinical and Clinical Studies**

LOCATION OF THE RESEARCH ACTIVITY (INSTITUTION/DEPARTMENT):
Department of pharmacy, University of Naples Federico II

TUTOR: Claudia Conte

PROPOSED RESEARCH ACTIVITIES (max 300 words): Triple-negative breast cancer (TNBC) is an aggressive phenotype of breast cancer. To tackle TNBC, combination therapies delivered through nanotechnologies can offer a powerful solution. Nanoparticles (NPs) functionalized with a poly(ethylene glycol) (PEG) coating ensure immune escape and long circulation that favour accumulation in the solid tumor but decrease NP uptake into cancer cells. Consequently, the treatment becomes poorly effective. In parallel, after iv administration, NPs functionalized with a targeting element interact with blood proteins that cover the surface, hampering receptor recognition and making the functionalization strategy useless. We hypothesise that targeted NPs to CD44 receptor overexpressed on TNBC cells can accumulate in tumors where the PEG coating is cleaved in response to specific stimuli the targeting element is exposed and recognized by the receptors, finally accumulating drug payload in cells. We also hypothesise that stimuli-sensitive NPs can be applied for the precision delivery of conventional

anticancer drugs in combination with siRNA to synergize chemotherapy. The PhD student will be involved in the development of PEG-sheddable stimuli-sensitive NPs targeted to the CD44 receptor able to accumulate in cancer cells. The nanoplatform will be applied to two therapeutic concepts consisting of delivering Docetaxel (DTX) as a conventional anticancer drug combined with a therapeutic siRNA against βIII tubulin to overcome DTX resistance or a siRNA against PD-L1 as combined chemo/immunotherapy strategy. Stimuli-sensitive PEG- poly(lactic-co-glycolic acid) PLGA block copolymers will be synthesized. NPs will be prepared through nanoprecipitation and scaled-up by microfluidic. The critical quality attributes of NPs (size, polydispersity index, zeta potential, encapsulation efficiency, drug release rate) will be tested in experimental conditions mimicking the biological environment. Cell internalization, cytotoxicity and gene silencing of NPs will be evaluated in 2D and 3D TNBC models.